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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,121	DEITERS ET AL.	
	Examiner	Art Unit	
	KAGNEW H. GEBREYESUS	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43, 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse dated June 12, 2009 in reply to the Office Action dated December 09, 2008 is acknowledged. Claims 1-39, 44, 45, 52-61 have been cancelled in the instant application. Claims 40-43 and 47-51 with the elected species of SEQ ID NO: 54 are present for examination.

All objections and rejections not reiterated in the instant Office Action are hereby withdrawn.

Claim Objections

Claim 41 is objected to because of the following informalities: Does the recitation:

"…the O-tRNA produced in a cell by cellular processing of a nucleic acid corresponding to SEQ ID NO: 65…"

imply the 'O-tRNA is expressed from the nucleic acid of SEQ ID NO: 65? Appropriate correction is required to clarify the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 42, 43, 47-51 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is because the specification lacks written description with regards to the structure of the unnatural amino acids comprising any alkynyl or azido group used with the O-RS molecule of SEQ ID NO: 54 and polynucleotides encoding said O-RS molecule.

The specification teaches a eukaryotic cell comprising the structure of the O-RS of SEQ ID NO: 54 that aminoacylates the O-tRNA of SEQ ID NO: 65 with p-propargyloxyphenylalanine (pPRphe), a single alkynyl unnatural amino acid.

The specification does not describe that the O-RS of SEQ ID NO: 54 or the O-RS that is encoded by SEQ ID NO: 26 preferentially aminoacylate any O-tRNA or the O-tRNA of SEQ ID NO: 65 with unnatural amino acids comprising any alkynyl or azido moiety. Eukaryotic cells comprising the specific O-RS and O-tRNA together with unnatural amino acids that broadly encompass any alkynyl or azido moieties are not described in the specification.

Moreover, claims 40, 41 encompass O-RS molecules with 90% identity to any naturally occurring TyrRS with at least 2 mutations at selected positions and that retain preferential aminoacylation of an unnatural amino acid comprising any alkynyl or azido moiety. The specification teaches a few ORS molecules such as the ORS of SEQ ID NO: 54 that aminoacylates the O-tRNA of SEQ ID NO: 65 with para-propargyloxyphenylalanine (pPRphe). However the specification does not teach an O-RS with up to 10% variation in sequence relative to 'any naturally occurring O-RS' and retains the above activities.

At the time the instant invention was filed, Applicants were not in possession of the above broadly claimed Tyr-ORS variants in eukaryotic cells. The art teaches that O-RS molecules with specific structures can only preferentially aminoacylate a specific type of unnatural amino acid (in the instant case, the O-RS of SEQ ID NO: 54 aminoacylates the O-

tRNA of SEQ ID NO: 65 with the unnatural amino acid comprising a single alkynyl moiety (p-propargyl-phenylalanine)).

The specification and the art further teach that specific O-RS molecules that preferentially aminoacylate corresponding O-tRNA with a specific unnatural amino acid are identified empirically using a screening methods. Thus at the time the instant invention one skilled in the art would not be able to predict the structures of an O-RS with up to 10% variation relative to the structure of an undefined O-RS from any source and the specific type of unnatural amino acid comprising any alkynyl or azido moiety.

Given this lack of description of representative species encompassed by the claimed genus, the specification fails to sufficiently describe the invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 40-43, 47-51 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for eukaryotic cells comprising O-RS molecules comprising SEQ ID NO: 54 and O-RS molecules encoded by SEQ ID NO: 26 that aminoacylates a corresponding O-tRNA (SEQ ID NO: 65) with para-propargyloxyphenylalanine (pPR-1), does not reasonably provide enablement for eukaryotic cells comprising any ORS molecule including SEQ ID NO: 54, conservative variants and any ORS that is at least 90% identical to any E. coli Tyr-tRNA synthetase (TyrRS) wherein said O-RS molecules aminoacylate any O-tRNA with any unnatural amino acid.

Applicants have amended the claims by cancelling the term 'conservative variants' and limiting the type of unnatural amino acids to be aminoacylated. However the claims still encompass unnatural amino acid comprising any alkynyl or azido moiety thus unnatural amino acids comprising a sub-genus of alkynyl or azido moieties.

However the specification does not enable a eukaryotic cell comprising a genus of ORS/OtRNA molecules where the ORS molecules can preferentially aminoacylate corresponding O-tRNAs with an unnatural amino acid comprising any alkynyl or azido moiety.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is directed to eukaryotic cells comprising specific ORS molecules (e.g. SEQ ID NO: 54-63) and corresponding amber suppressor $tRNA_{CUA}$ (O-tRNA of SEQ ID NO: 65) wherein said ORS molecules can preferentially aminoacylate said O-tRNA with para-propargyloxyphenylalanine (pPRO-Phe) or the ORS molecules of SEQ ID NO: 48-53 and corresponding amber suppressor $tRNA_{CUA}$ wherein said ORS molecules can preferentially aminoacylate said O-tRNA with the azido unnatural amino acid depicted in fig. 11, number 2.

The state of the prior art teaches that preferential aminoacylation with any specific unnatural amino acid requires the use of specific ORS molecules (or group of ORS molecules with common structural characteristics) and a corresponding amber suppressor O-tRNA molecule for incorporation of a specific unnatural amino acids into a protein.

However the claims are drawn to eukaryotic cells comprising an ORS molecule of SEQ ID NO: 54, or a protein with at least 90% identity to any naturally occurring Tyr-RS that

comprises at least two changes at positions corresponding to position Tyr37, Asn126, Asp182, Phe183 and Leu186 at a position corresponding to *E. coli* tyrosyl tRNA synthetase and that preferentially aminoacylate any O-tRNA (claim 40) or the O-tRNA of SEQ ID NO: 65 (claim 41) with an unnatural amino acid comprising any alkynyl or azido moiety.

The specification, supported by the prior art teaches that aminoacylation specificity of orthogonal tRNA synthetases (O-RS) to specific unnatural amino acids results from structural modification introduced in the amino acid binding pocket and/or other regions of a native tRNA synthetase. Such ORS will differ from their native counterparts by acquiring increased specificity for an unnatural amino acid compared to specificity for their natural amino acid substrates. However neither the prior art nor the instant specification teach how to make or use eukaryotic cells comprising any specific O-RS including the O-RS of SEQ ID NO: 54, that can acquire the ability to aminoacylate any possible unnatural amino acid comprising any alkynyl or azido moiety onto an O-tRNA.

Furthermore claims 47-51 encompass any polynucleotide that hybridizes to SEQ ID NO: 26 over substantially the entire length of the nucleic acid. The specification defines the term "substantially" as follows:

> The phrase "substantially identical," in the context of two nucleic acids or polypeptides (e.g., DNAs encoding an O-tRNA or O-RS, or the amino acid sequence of an O-RS) refers to two or more sequences or subsequences that have at least about 60%, preferably 80%, most preferably 90-95% nucleotide or amino acid residue identity…"

However the specification does not teach how to make or use any polynucleotide sequence with up to 40% variation to the polynucleotide sequence of SEQ ID NO: 54 (the elected species).

The art teaches that mutations at positions other than the amino acid binding pocket of an ORS can bring about changes in amino acid specificity. For example US 5,370,995 (Hennecke et al) teaches that a mutation at position 294 of *E. coli* phenylalanine tRNA synthetase results in altered specificity. Hennecke et al teach that an alanine to glycine substitution at position 294 (Gly294) results in incorporation of para-fluoro-phenylalanine instead of phenylalanine into a protein.

Furthermore claim 42 (e) encompass O-RS polypeptides with at least 20 contiguous amino acids.

However applicants have not taught how to make and how to use the scope of all possible ORS fragments or polynucleotides encoding the same. For example one of skill would not know how to use a polypeptide with at least 20 contiguous amino acids wherein said fragment comprises the variation at position 126 and position 182.

Furthermore claims 42 and 43 also encompass any polypeptide that is specifically immunoreactive with an antibody specific for a polypeptide of SEQ ID NO: 54 (elected species). However while certain truncated variants of SEQ ID NO: 54 such as fragments containing the same epitopes derived from SEQ ID NO: 54 may immunoreact with an antibody for SEQ ID NO: 54, the specification does not teach how to make and use all possible polypeptide variants that immunoreacts with an antibody specific for SEQ ID NO: 54.

Without sufficient guidance, determination of eukaryotic cells comprising the specific structure of the ORS molecules or ORS with at least 90% identity to any naturally occurring Tyr-RS that further comprises at least two changes at positions corresponding to position Tyr37, Asn126, Asp182, Phe183 and Leu186 at a position corresponding to *E. coli* tyrosyl tRNA

synthetase and that preferentially aminoacylate any O-tRNA or the O-tRNA of SEQ ID NO: 65 with any unnatural amino acid comprising any alkynyl or azido moiety is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40-43, 47-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 52-54, 56-59, 62-64 of copending Application No. 10/826,919. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method used in application 10/826,919 requires the eukaryotic cells disclosed in the instant application thus rendering the claims in the instant application obvious. Furthermore application 10/826,919 discloses the same O-RS

molecule (SEQ ID NO: 54) and species of unnatural amino acid comprising an alkynyl moieties (parapargyloxy-phenylalanine) as the claims in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Applicant's amendment cancelling claims 52-61 necessitated the new ground(s) of rejection on the ground of nonstatutory obviousness-type double patenting presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANDREW WANG can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus/
Examiner, Art Unit 1656
9/16/2009

/Andrew Wang/
Supervisory Patent Examiner, Art Unit 1656